Epidemiology of Brain Lymphoma Among People With or Without Acquired Immunodeficiency Syndrome

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Background: **In recent years, brain lymphoma incidence has dramatically increased, presumably because of elevated risk of brain lymphoma among persons with acquired immunodeficiency syndrome (AIDS).** ***Purpose:*** **The objective of this study was to estimate independent incidence and survival rates of brain lymphoma among persons with or without AIDS and to understand the epidemiologic features of this cancer.** ***Methods:*** **We linked AIDS and cancer registry reports at nine state and local health departments and compared the demographics, histology, and survival of brain lymphoma cases among persons with or without AIDS. The data were limited to people under 70 years of age. We calculated the incidence of brain lymphoma among persons with AIDS and compared observed cases with those expected. The differences were statistically analyzed using the Poisson test. Epidemiologic features of brain lymphoma in persons with or without AIDS were compared using the chi-squared test, the Student's *t* test, and the chi-squared test for linear trend. The logrank test was used to compare survival rates estimated by the Kaplan–Meier technique. All *P* values were two-sided.** ***Results:*** **We matched 50 989 AIDS registry reports to 859 398 cancer registry reports (data from 1981 to 1990) and found 431 people with both AIDS and brain lymphoma. Among people with AIDS, those developing brain lymphoma versus those without brain lymphoma were more likely to be white (70% versus 59%; *P*<.001) and had homosexuality as their only human immunodeficiency virus risk factor (75% versus 64%; *P*<.001). Of the 431 patients, 223 developed brain lymphomas during 47 465 person-years of observation after diagnosis of AIDS. The absolute incidence rate of brain lymphoma among persons with AIDS was 4.7/1000 person-years (95% confidence interval = 4.1-5.3/1000 person-years), 3600-fold higher than the base-line rate in the general population. From 1980 through 1989, overall counts of brain lymphoma increased ninefold. Most of this increase was derived from persons with AIDS, but a substantial increase also occurred among persons without AIDS (0.04/100 000 in 1982 to 0.28/100 000 in 1989) (chi-squared test for trend; *P*<.05). The median survival was shortest for persons with AIDS and brain lymphoma (2 months), was intermediate for persons with brain lymphoma without AIDS (5-7 months), and was longest for persons with AIDS without brain lymphoma (14 months) (*P*<.05 for all comparisons).** ***Conclusions:*** **This analysis distinguishes the separate epidemiologies of brain lymphoma incidence among persons with or without AIDS and shows brain lymphoma incidence among persons with AIDS to be several thousand-fold higher than that in the general population. The study documents the overwhelming effect of AIDS-associated brain lymphoma on the overall rate in the general population and demonstrates a significantly rising trend, although of a lesser magnitude, among persons without AIDS.** ***Implications:*** **This study emphasizes a greater need to bring health care resources to this burgeoning epidemic. [J Natl Cancer Inst 1996;88:675-9]**

In recent years, the incidence of brain lymphoma has risen dramatically (*1-3*), as has non-Hodgkin's lymphoma more generally (*4-6*). Infection with the human immunodeficiency virus (HIV) increases risk of developing brain lymphoma; brain lymphoma in an HIV-positive person meets the Centers for Disease Control and Prevention's surveillance definition for acquired immunodeficiency syndrome (AIDS) (*7*). Brain lymphomas among people with AIDS are thought to represent much of the recent increase; the risk of brain lymphoma in patients with AIDS, however, has not been accurately measured. Cancer registries do not include information on HIV status or AIDS, and AIDS registries do not contain information on all cases of brain lymphoma among persons with AIDS. Therefore, since the AIDS epidemic began in 1981, neither routine surveillance of cancer nor of AIDS measures the incidence of brain lymphoma among persons with or without AIDS.

Description of trends in brain lymphoma incidence is complicated by changes in diagnostic imaging technologies and disease classification. The use of computerized axial tomography and nuclear magnetic resonance imaging could have artifactually increased case counts, as could the reclassification in the early 1980s of microgliomas as primary brain lymphomas (*8*). Nevertheless, Eby et al. (*2*) showed that for the period 1973-1984, these factors could not account for the magnitude of increased reports.

To examine the occurrence of brain lymphoma among persons with or without AIDS, we linked AIDS and cancer registries at state and local health departments in the United States. This approach permitted a population-based description of brain lymphoma without the referral biases inherent in case series and permitted determination of the risk of brain lymphoma among people with AIDS relative to that of the general population. The objective of this study was to estimate independent incidence and survival rates of brain lymphoma among persons with or without AIDS and to understand other epidemiologic features of these groups.

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See "Notes" section following "References."

Materials and Methods

We linked cases from AIDS and cancer registries for the entire states of California (six sites), Florida, and New Jersey and metropolitan Atlanta. Data were limited to people under 70 years of age to enhance the feasibility of personal computer-based linkage. This restriction eliminated more than one half of the cancer registry cases but less than 5% of the AIDS registry cases, thereby facilitating linkage operations in the field. Therefore, no information on AIDS or cancer is available for people over 70 years of age. We limited analyses to brain lymphoma cases occurring in time periods where the data were considered complete in both the AIDS and cancer registries, generally 1981-1990, although cancer registry data were not available for all years in all regions. Cases of brain lymphoma reported to cancer registries that did not link to an AIDS record were assumed to represent brain lymphoma among persons without AIDS. The methods of linkage have been previously described (9).

We defined brain lymphoma as an initial AIDS-defining illness when 1) the AIDS registry recorded it as such or 2) a linked cancer record showed brain lymphoma diagnosed during the month of AIDS diagnosis or up to 1 year earlier. We tabulated cases of brain lymphoma among persons with AIDS in one or the other registry or in both. We then compared the histology by Working Group Classification (*8,10*), tumor site, and actuarial survival (*11*) of brain lymphoma cases by AIDS status. Although cases of brain lymphoma were counted for persons with AIDS in all registry sites, counts of brain lymphoma among persons without AIDS were available only from San Francisco and Atlanta; these locations participated in the Surveillance, Epidemiology, and End Results (SEER) Program[1] of the National Cancer Institute (*12*). Therefore, we compared brain lymphomas among persons with AIDS from all registry sites to brain lymphomas among persons without AIDS in San Francisco and Atlanta.

We estimated the risk of brain lymphoma among persons with AIDS compared with the general population as the standardized incidence ratio (SIR) of brain lymphoma (i.e., the quotient of observed and expected cases of brain lymphoma after AIDS diagnosis). Expected cases were computed by multiplying the age-, sex-, and race-specific rates of brain lymphoma among persons without AIDS during the period 1981-1989 (San Francisco and Atlanta) or 1975-1980 (all standard SEER registries) by the person-years that all persons with AIDS were observed (the time from AIDS diagnosis until death, the end of complete cancer registration, or brain lymphoma diagnosis, whichever occurred sooner). Although death reporting was generally complete, follow-up was censored at 3.5 years to avoid spurious accrual of person-years among persons with AIDS with unreported deaths; 1491 cases or 2.9% of all persons with AIDS were so censored. Statistical differences between observed and expected cases were detected by the Poisson test with two-tailed P value.

To determine whether imperfect linkage caused misclassification of persons with AIDS as persons without AIDS, we compared the age, sex, race, and survival of persons without AIDS diagnosed with brain lymphoma before the AIDS epidemic (1975-1980) with persons without AIDS diagnosed in 1981-1989 in San Francisco and Atlanta. To describe trends in brain lymphoma among persons with AIDS, persons without AIDS, and the population as a whole, we plotted case reports and age-, sex-, and race-adjusted rates (using the 1980 U.S. census) for San Francisco and Atlanta.

Comparisons of epidemiologic features of brain lymphoma in persons with or without AIDS were made with the chi-squared test, the Student's t test, and the chi-squared test for linear trend. The Kaplan–Meier technique was used to estimate survival and statistical comparisons made with the logrank test.

Results

We compared 50 989 AIDS registry reports to 859 398 cancer registry reports in common time periods (1981 through 1990) and found 431 persons with both AIDS and brain lymphoma. As shown in Table 1, of the 208 brain lymphoma cases diagnosed at the time of AIDS diagnosis, 192 (121 + 71; 92%) were reported to an AIDS registry. Only 269 (139 + 130; 62%) of all 431 cases were reported to cancer registries; however, this was somewhat higher (123 + 59; 81.6%) for brain lymphoma when diagnosed subsequent to AIDS.

Cases of brain lymphoma among people without AIDS diagnosed in 1975-1980 were not significantly different ($P>.05$) from those diagnosed in 1981-1990 when compared by age (median age, 57 versus 55 years), sex (female, 39% versus 39%), race (white, 91% versus 73%), or survival (median survival, 7 versus 5 months).

As shown in Table 2, people with AIDS and brain lymphoma were more likely to be white (70% versus 59%; $P<.001$) and have homosexuality as their only risk factor for HIV (75% versus 64%; $P<.001$) than people with AIDS without brain lymphoma. There was no significant difference in the rates of brain lymphoma among persons with AIDS in different cities and states. Compared with cases of brain lymphoma without AIDS from 1975 to 1990, persons with AIDS and brain lymphoma were younger (median age, 37 versus 56 years) and more likely to be black (14% versus 5%; $P<.001$) and male (96% versus 61%; $P<.001$). As shown in Fig. 1, the median survival was shortest for persons with AIDS and brain lymphoma (2 months), was intermediate for persons with brain lymphoma without AIDS (5-7 months), and was longest for persons with AIDS without brain lymphoma (14 months) ($P<.05$ for all comparisons).

The histologic grade and anatomic site of brain lymphoma could be evaluated in 269 persons with AIDS and the 142 (54 in 1981-1990 and 88 in 1975-1980) persons without AIDS with cases reported to cancer registries (Table 3). Microscopic confirmation was indicated in cancer registry reports for 88% of the persons (236 of 269) with AIDS and for 98% of the persons (139 of 142) without AIDS. Histologic grade for brain lymphomas among persons without AIDS diagnosed in 1975-1980 differed from those diagnosed in 1981-1990 because of changes in histologic classification systems. Reports of brain lymphomas among persons with AIDS were more likely than those among persons without AIDS to have not otherwise specified (NOS) anatomic site within the brain (35% versus 17% or 16%) and/or NOS histology (51% versus 32% or 14%). Among cases where histologies were specified, working formulation grades (high, medium, and low) were not significantly different between persons with or without AIDS diagnosed in the same time period (1981-1990) (Table 3).

Table 1. Cases of brain lymphoma among people with acquired immunodeficiency syndrome (AIDS) found through linkage of AIDS registries and cancer registries during 1981-1990

	Cases reported to			
	AIDS registry only	Cancer registry only	Both registries	Total
Brain lymphoma				
Diagnosed at initial AIDS diagnosis	121	16	71	208
Diagnosed subsequent to AIDS diagnosis	41	123	59	223
Total	162	139	130	431

Table 2. Demographics and human immunodeficiency virus (HIV) risk group of people with acquired immunodeficiency syndrome (AIDS) and/or brain lymphoma

Demographic	AIDS with brain lymphoma,* 1981-1990		AIDS without brain lymphoma,* 1981-1990		Brain lymphoma without AIDS,†,‡ 1975-1990	
	No. of patients	%	No. of patients	%	No. of patients	%
Median age, y§	37		Not available		56	
Race						
White	300	70	29 800	59	119	84
Black	61	14	13 939	28	7	5
Hispanic	62	14	6288	12	7	5
Other/unknown	8	2	531	1	9	6
Total	431	100	50 558	100	142	100
Sex						
Male	413	96	45 839	91	87	61
Female	18	4	4719	9	55	39
Total	431	100	50 558	100	142	100
HIV risk group						
Homosexual contact	324	75	32 385	64	*	*
Intravenous drug user	44	10	8126	16	*	*
Both	29	7	3821	8	*	*
Heterosexual contact	15	4	3222	6	*	*
Other risk factors‖	19	4	3004	6	*	*
Total	431	100	50 558	100	*	*

*States of California (six sites), Florida, and New Jersey and metropolitan Atlanta.
†San Francisco and metropolitan Atlanta; cases diagnosed from 1981 to 1989 and 1981 to 1990, respectively.
‡All SEER regions (Connecticut, Iowa, New Mexico, Utah, Hawaii, metropolitan areas of Detroit, San Francisco–Oakland, Atlanta, and Seattle–Puget Sound). Cases were diagnosed from 1975 to 1980.
§For case patients under 70 year old.
‖Other risk factors = transfusion, pediatric AIDS, unassigned.

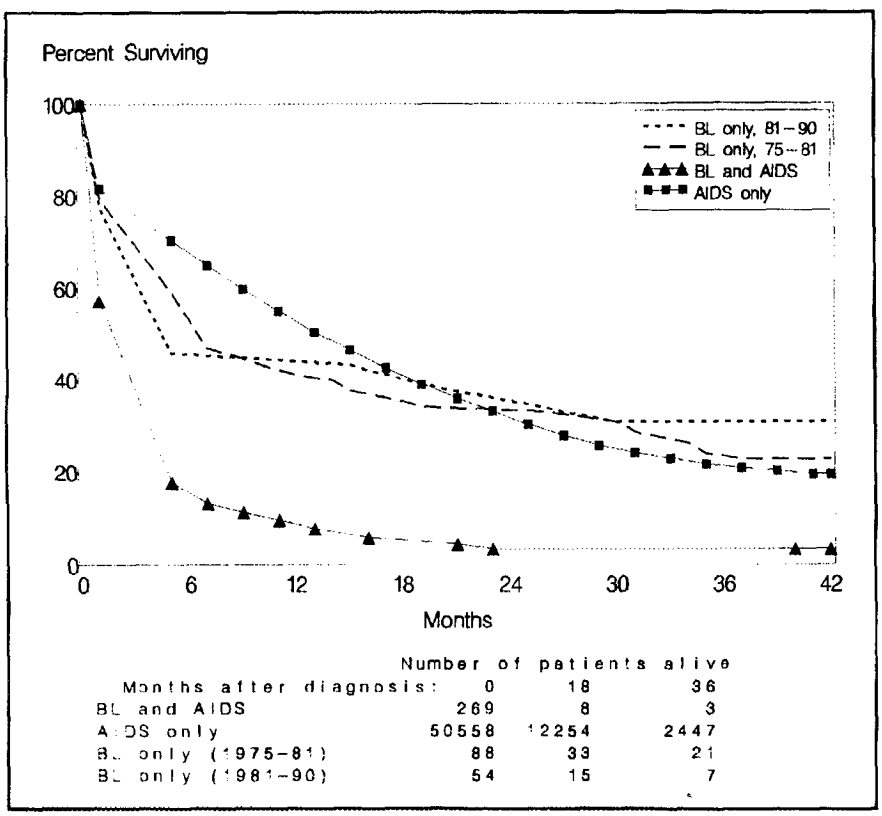

Fig. 1. Life test survival analysis of people with AIDS and brain lymphoma, people with AIDS only, and people with brain lymphoma only (diagnosed in 1975-1981 or 1981-1990) ($P<.05$ for all comparisons). BL = brain lymphoma.

Incidence and Risk of Brain Lymphoma Among Persons With AIDS

Brain lymphoma was diagnosed at initial AIDS diagnosis in 208 (48%) case patients (0.4% of 50 989 persons with AIDS) and was subsequent to another AIDS-defining illness in 223 case patients (Table 1). The 223 case patients developed brain lymphoma during 47 465 person-years of observation after AIDS diagnosis (1981-1990). Thus, the absolute incidence of brain lymphoma among persons with AIDS was 4.7/1000 person-years (i.e., 223/47 465 person years; 95% confidence interval = 4.1-5.3/1000 person-years).

During the 47 465 person-years of observation, 1981-1990 base-line incidence predicted 0.0617 expected cases; thus, the standardized incidence ratio was 3.61×10^3 (i.e., 223/0.0617). The base-line incidence from the years 1975-1980 predicted even fewer cases, 0.0287; thus, the standardized incidence ratio was equal to 7.77×10^3.

Fig. 2 shows cases and age-adjusted rates of brain lymphoma among persons with or without AIDS in San Francisco and Atlanta in 1975-1989. By 1984, cases of brain lymphoma among persons with AIDS exceeded those among persons without AIDS. In 1989, the overall counts of brain lymphoma were ninefold those of 1980. While most of this increase derived from cases among persons with AIDS, the incidence of brain lymphoma among persons without AIDS increased from 0.04/100 000 person-years in 1982 to 0.28/100 000 person-years in 1989 (chi-squared test for trend, $P<.05$).

Discussion

This is the first analysis that is clearly able to distinguish the separate epidemiologies of brain lymphoma among people with or without AIDS. By linking AIDS and cancer registries, we measured brain lymphoma incidence among people with AIDS and found it to be several thousand-fold that observed in the general population. Measurement of brain lymphoma risk among all HIV-infected persons, not only those with AIDS, would have been preferable, but dates of seroconversion were unavailable. We found the same risk factors (older age, white race, male sex, and homosexuality as

Table 3. Tumor site and histology by working formulation (WF) grade of people with brain lymphoma with or without acquired immunodeficiency syndrome (AIDS)

	AIDS with brain lymphoma,* 1981-1990		Brain lymphoma without AIDS,† 1981-1990		Brain lymphoma without AIDS,‡ 1975-1980	
	No. of patients	%	No. of patients	%	No. of patients	%
Site						
Cerebrum	122	45	33	61	50	57
Cerebellum	15	6	4	7	8	9
Other brain§	39	14	8	15	16	18
Brain NOS‖	93	35	9	17	14	16
Total	269	100	54	100	88	100
Histology (by WF grade)						
High	55	20	13	24	3	3
Medium	72	27	17	32	41	47
Low	5	2	4	7	5	6
Miscellaneous¶	1	0	3	5	27	31
NOS	136	51	17	32	12	14
Total	269	100	54	100	88	100

*States of California (six sites), Florida, and New Jersey and metropolitan Atlanta.
†San Francisco and metropolitan Atlanta.
‡All SEER regions (Connecticut, Iowa, New Mexico, Utah, Hawaii, metropolitan areas of Detroit, San Francisco–Oakland, Atlanta, and Seattle–Puget Sound).
§Other brain = ventricles, tapetum, brain stem.
‖NOS = not otherwise specified.
¶Histology = microglioma, mycosis fungoides, T-cell lymphoma, and others (*10*).

only HIV risk group) for brain lymphoma among persons with AIDS as have been shown more generally for non-Hodgkin's lymphoma among persons with AIDS. We documented here the overwhelming effect that the HIV epidemic has had on brain lymphoma rates for the general population, but we also demonstrated a significantly rising trend in brain lymphoma among persons without AIDS.

This last conclusion should be tempered by concern that imperfect linkage could introduce bias if unlinked brain lymphomas were erroneously classified as occurring in persons without AIDS. The case for substantial misclassification is not supported by comparison of persons without AIDS with brain lymphoma before versus during the AIDS epidemic: in measures of age, sex, race, and survival, both groups of persons without AIDS were similar to each other but dissimilar from persons with AIDS and brain lymphoma. Our finding of increases in brain lymphoma among persons without AIDS younger than 70 years of age mirrors a similar increase documented among the older general population (*13*).

The etiology of brain lymphoma among persons with or without AIDS remains unknown, but our findings are consistent with a second viral cause, suggested by MacMahon et al. (*14*), who demonstrated Epstein–Barr virus in brain lymphoma from people with AIDS. In addition, recently discovered herpes-like viral sequences have been found in Kaposi's sarcoma (*15*) and body-cavity-based non-Hodgkin's lymphoma (*16*). Increased transmission among persons with AIDS of a viral agent etiologic for brain lymphoma might be expected to increase rates among susceptible subgroups of persons without AIDS. Certainly, this is only one of several etiologic possibilities; future collaborations of epidemiologists, virologists, and molecular biologists may support or refute this hypothesis.

Overlapping information in the registries allowed for an independent determination of their completeness. As shown with Kaposi's sarcoma (*9*), AIDS registries are generally complete for AIDS-defining cancers, but cancer registries may not obtain all cases of cancer among persons with AIDS because of the mistaken belief that the information in an AIDS registry case report satisfies the obligation to report the cancer.

In summary, this analysis of linked AIDS and cancer registries measured the incidence of brain lymphoma among persons with AIDS to be 4.7/1000 person-years (1981-1990), a rate 3.6×10^3 to 7.8×10^3 times higher than in the general population. Brain lymphoma among people with AIDS now represents most cases of brain lymphoma in the general population. For unknown reasons, the rate

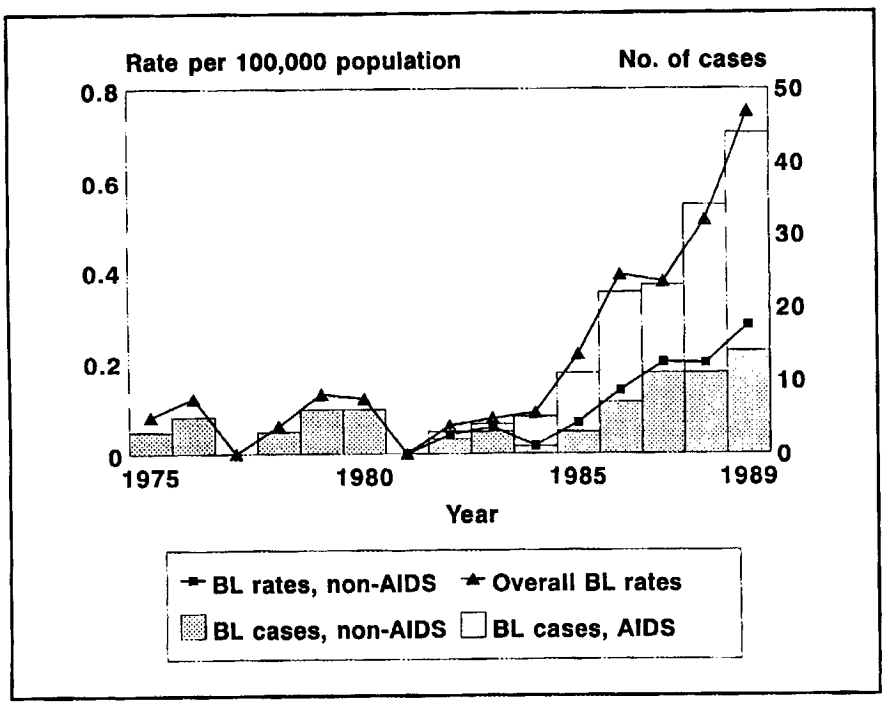

Fig. 2. Case counts and rates of brain lymphoma among people with or without AIDS in 1975-1989 (San Francisco and Atlanta). BL = brain lymphoma.

of brain lymphoma among people without AIDS also appears to be rising rapidly.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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